REMARKS

Claims 1, 5-12, 14-20, 77-85, 88-94, 101-114, 116-127 and 130-194 are currently pending. Claims 133-194 have been added. Claims 2-4, 13, 21-76, 86-87, 95-100, 115 and 128-129 have been cancelled. Claims 1, 9, 11, 14-16, 18, 77-85, 88-94, 101-103, 107-112, 114 and 116-127 have been amended. Support for the amendment to claims 18, 80, 89, 111 and 121 can be found in paragraphs 37, 56, 77, 121, 122, and elsewhere in the application. Support for the amendments to claims 1, 101 and 102 can be found in paragraphs 52, 53, 122, 133, 143 and elsewhere in the application. The amendments to claims 9, 11, 14-16, 78-79, 81-85, 88, 90-94, 107-109, 116-120 and 122-127 were made to correct grammatical and typographical errors. The amendments to claims 103, 107, 110, 112, 114 and 116-119 were made to add claim dependencies. Support for the new claims can be found throughout the specification. Therefore, no new matter has been added.

Supplemental Information Disclosure Statement

Applicants are filing concurrently herewith a Supplemental Information Disclosure Statement and Form 1449 in order to notify the examiner of copending U.S. Application Serial No. 10/873,856 and to make the Office Actions and responses in said application of record in this application.

Double Patenting Rejection

The examiner has issued a double patenting rejection and advised applicants that should claim 1 be found allowable that claim 101 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof.

Although applicants disagree with this double patenting rejection, claims 1 and 101 have been amended so that the scope of the claims is different. Specifically, the type of transcription template in each claim is different.

As a result, applicants submit that claims 1 and 101 do not violate the judicially created doctrine of double patenting or 37 C.F.R. § 1.75. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 111 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the examiner states that it is unclear how the unsubstituted GMP can be a substituted guanosine, as the two are mutually exclusive.

In order to expedite prosecution of the instant application, applicants have amended claim 111 to delete the phrase "substituted guanosine or". Applicants believe that the amended claim addresses the examiner's concern. Please note that applicants have also made the same amendment in claim 18.

As a result, applicants submit that amended claim 111 (and claim 18) satisfies 35 U.S.C. § 112, second paragraph. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 5-17, 19-21, 77-96, 101-120 and 122-132 stand rejected under 35 U.S.C. § 103(a) as being obvious over Pieken *et al.* (U.S. Patent No. 5,660,985), Brieba *et al.* (Biochemistry (2000) 39:919-923) and Sousa *et al.* (U.S. Patent No. 6,107,037).

Applicants respectfully disagree.

The Claimed Invention

The invention relates to materials and methods for enzymatically producing pools of randomized oligonucleotides having modified nucleotides including 2'-OMe GTPs from which aptamers to a specific target can be selected. In a preferred embodiment, the invention relates to pools of r/mGmH nucleic acids, which are oligonucleotides containing 2'-OMe A's, U's or T's, C's and G's, where up to 10% of the G's are ribonucleotides.

Differences Between the Claimed Invention and the Cited Art

The examiner states that Pieken discloses a method for identifying nucleic acid ligands that bind to a target molecule wherein the nucleic acid ligands comprise a 2'-OMe modified nucleotide. Assuming, arguendo, that the examiner is correct, Pieken neither discloses nor suggests applicants' method, particularly in that applicants' method requires not just the use of both Mg and Mn ions, but the use of both wherein the concentration of Mg ions is about 3 to 5 times greater than the concentration of Mn ions.

Furthermore, the transcription reaction of Pieken does not teach the use of a modified RNA polymerase or the use of 2'-OH GTP.

Applicants submit that the deficiencies of Pieken are not cured by Brieba. Brieba does not teach the use of one or more 2'-OMe NTPs, 2'-OH GTP, or a ratio of magnesium ions to manganese ions of about 3-5 to 1. Brieba also does not relate to the SELEX method.

Applicants further submit that the deficiencies of Pieken are not cured by Sousa. Column 15, lines 44-48 of Sousa state that transcription reactions were carried out in 40 mM Tris-Cl pH 8.0, 15 MM $MgCl_2$ and 5 mM DTT **or** 20 mM Manganese Citrate pH 8.0, 5 mM DTT at 37°C. That is, two separate transcription reactions were used. One transcription reaction was carried out in 40 mM Tris-Cl pH 8.0, 15 MM $MgCl_2$ and 5 mM DTT. The other

transcription reaction was carried out in 20 mM Manganese Citrate pH 8.0 and 5 mM DTT. As a result, Sousa uses transcription buffer with either magnesium or manganese, but not both. In fact, Sousa states this throughout the reference. See, for example, column 22, line 18; col. 22, line 34; col. 24, line 49; col. 24, line 51; Table I; Table II; Table V; and col. 31, lines 22-25.

In addition, Sousa does not teach an embodiment wherein the concentration of magnesium ions is about 3 to 5 times greater than the concentration of manganese ions. In fact, the concentration of magnesium ions in one embodiment of Sousa is 15 nM while the concentration of manganese ions is 20 nM in another embodiment. As noted above, Sousa uses magnesium or manganese separately so no ratio of Mg to Mn exists. However, if Sousa used Mg and Mn together, the ratio of Mg to Mn would be 0.75:1.

Furthermore, Sousa does not teach the use of 2'-OMe NTPs or 2'-OH guanosine triphosphate. Sousa also does not relate to the SELEX method.

In order to support the patentability of the claims, applicants submit herewith a Declaration under 37 C.F.R. § 1.132, along with Exhibit A, which clearly demonstrate the importance of using both magnesium and manganese in specific concentrations in transcription reaction mixtures for incorporating 2'-OMe NTPs, especially 2'-OMe GTPs, into nucleic acid ligands using the SELEX process.

Specifically, applicants tested a variety of Mg and Mn concentrations, individually and in combination, in transcription reaction mixtures to determine what effect the Mg and Mn concentrations would have on the ability of the modified polymerase to incorporate 2'-OMe NTPs into nucleic acid ligands using the iterative SELEX process.

Exhibit A shows that when Mg is used alone, the incorporation of 2'-OMe NTPs into nucleic acid ligands using the SELEX process is extremely inefficient or non-existent and

produces very low or no yield of transcripts. Exhibit A also shows that when Mn is used alone, the incorporation of 2'-OMe NTPs into nucleic acid ligands using the SELEX process is extremely inefficient or non-existent and produces very low or no yield of transcripts. In addition, Exhibit A shows that when Mg and Mn are used in combination, in a ratio of Mg to Mn of about 3-5 to 1, the incorporation of 2'-OMe NTPs into nucleic acid ligands using the SELEX process is extremely efficient and produces a very high yield of transcripts. Furthermore, when the ratio of Mg to Mn falls outside of the about 3-5 to 1 range, the incorporation of 2'-OMe NTPs into nucleic acid ligands using the SELEX process is not nearly as efficient and the yield of transcripts is low.

The transcription reaction mixtures recited by the claims were carefully selected to produce oligonucleotide transcripts that contain 2'-OMe modified nucleotides, including at least one 2'-OMe GTP, for effective and efficient use in the SELEX process. Specifically, it is the combination of all of the reagents in the mixtures that produces a yield sufficient to be used in the SELEX process. As shown in Exhibit A, the transcription reaction mixture and conditions, including a specific ratio of magnesium ions to manganese ions, allow the modified RNA polymerases to accept all 2'-OMe NTPs as substrates and incorporate these modified nucleotides into the transcript during both the initiation and elongation portions of transcription. On the other hand, standard transcription conditions are not able to generate libraries of 2'-OMe transcripts because the polymerase is either not able to accept 2'-OMe nucleotides as substrates or the transcript terminates after the 2'-OMe NTP is incorporated. As a result, standard transcription conditions are not useful in the iterative SELEX process. In conclusion, it is only the specific combination of reactants in the claimed transcription reaction mixture that works to

incorporate any 2'-OMe nucleotides into transcripts with sufficient yield to be used in the iterative SELEX process.

Accordingly, applicants submit that after analyzing the cited references and the claimed invention, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 18, 89 and 121 stand rejected under 35 U.S.C. § 103(a) as being obvious over Pieken *et al.* (U.S. Patent No. 5,660,985), Brieba *et al.* (Biochemistry (2000) 39:919-923) and Sousa *et al.* (U.S. Patent No. 6,107,037) in view of Milligan *et al.* (Methods Enzymology (1989) 180:51-62).

Applicants respectfully disagree. As an initial matter, applicants note that the rejected claims are dependent claims. Milligan, however, when combined with the teachings of the previously cited references, does not cure the deficiencies of the previously cited references. Thus, for the reasons stated above regarding the use of both Mg and Mn ions in the specified ratio, applicants submit that the rejected claims are allowable.

In addition, Milligan does not teach the use of a modified RNA polymerase, one or more 2'-OMe NTPs or 2'-OH GTP. Milligan also does not relate to the SELEX method.

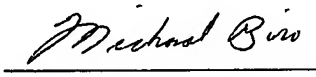
Accordingly, applicants submit that after analyzing the cited references and the claimed invention, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants submit that the claims are definite and are not obvious in view of the cited references. Accordingly, reconsideration of the rejections and allowance of the claims at an early date are earnestly solicited.

If there are any questions regarding this Amendment and Response or if the undersigned can be of assistance in advancing the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,



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REMARKS

This is a summary of the interview that occurred on September 25, 2008 in the above-captioned application. It should be noted that applicants interviewed the above-identified application (U.S. Application Serial No. 10/729,581) and its sibling application (U.S. Application Serial No. 10/873,856) concurrently. Both applications were interviewed together due to the similarity of the issues in each case and the similarity of the cited art in each case. Participants in the interview were: 1) examiner Mark Staples, who appeared in person (examiner for the '581 application); 2) examiner Stephanie Mummert, who participated by telephone (examiner for the '856 application); 3) John Harre, who appeared in person (applicants' representative); 4) Michael Biro, who appeared in person (applicants' representative); and Ivor Elrifi, who appeared in person (applicants' agent).

In accordance with 37 C.F.R. § 1.133 and M.P.E.P. § 713.04, applicants provide the following interview summary.

No exhibits were shown and no demonstrations were conducted.

All of the pending claims in each of U.S. Application Serial Nos. 10/729,581 and 10/873,856 were discussed.

The following cited references were discussed: Pieken (U.S. Patent No. 5,660,985), Brieba (Biochemistry (2000) 39:919-923), Sousa (U.S. Patent No. 6,107,037), Padilla (Nucleic Acids Research (2002) 30(24):e138), Milligan (Methods Enzymology (1989) 180:51-62) and Kujau (J. Biochem. Biophys. Methods (1997) 35:141-151).

Applicants agreed to amend the claims to recite concentrations of Magnesium and Manganese that overcome the cited art. Applicants also discussed other possible claim amendments.

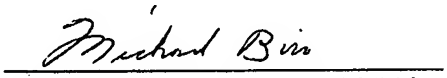
The general thrust of the principal arguments related to the above claim amendments.

No other pertinent matters were discussed.

Agreement with respect to the claims was not reached during the interview.

As a final note, applicants thank examiner Staples and examiner Mummert for allowing applicants to interview both the '581 and the '856 application together.

Respectfully submitted,



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